

Soft tissue sarcomas: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

P. G. Casali¹, L. Jost², S. Sleijfer³, J. Verweij³ & J.-Y. Blay⁴

On behalf of the ESMO Guidelines Working Group*

¹Department of Cancer Medicine, Istituto Nazionale dei Tumori, Milan, Italy; ²Department of Oncology, Kantonsspital, Bruderholz, Switzerland; ³Department of Medical Oncology, Erasmus University Medical Center, Rotterdam, The Netherlands; ⁴INSERM U590, Claude Bernard University and Department of Oncology, Edouard Herriot Hospital, Lyon, France

The following recommendations apply to adult-type soft tissue sarcomas arising from limbs and superficial trunk. Recommendations on retroperitoneal sarcomas, desmoid-type fibromatosis and uterine sarcomas are provided separately at the end of the chapter with regard to those main aspects by which they differ from more frequent soft tissue sarcomas. In general, the main principles of diagnosis and treatment may well apply to all soft tissue sarcomas, including the rarest presentations [e.g. visceral sarcomas other than gastrointestinal stromal tumors (GIST), head and neck sarcomas], which therefore are not specifically covered. Specific histological types, however, may deserve specific approaches, which may not be covered hereafter, given the scope of these Recommendations. Extraskelatal Ewing's family tumors and embryonal and alveolar rhabdomyosarcoma are covered by other ESMO Clinical Recommendations, inasmuch as they need completely different approaches. The same applies to GIST.

incidence

Adult soft tissue sarcomas are rare tumors, with an estimated incidence averaging 4/100 000/year in Europe.

diagnosis

The standard approach to diagnosis consists of multiple core needle biopsies. However, an excisional biopsy may be the most practical option for <5 cm superficial lesions. An open biopsy may be another option in selected cases. The biopsy should be

performed by a trained surgeon, or discussed between the surgeon and the radiologist. It should be planned in such a way that the biopsy pathway and the scar can be safely removed on definitive surgery, and should be preceded by imaging [contrast-enhanced magnetic resonance imaging (MRI) is the preferred method for limb and superficial trunk lesions].

Histological diagnosis should be made according to the World Health Organization (WHO) classification. The malignancy grade should be provided in all cases in which this is feasible based on available systems. In Europe, the Fédération Nationale des Centres de Lutte Contre le Cancer (FNLC) grading system is generally used, which distinguishes three malignancy grades. A core biopsy may underestimate the tumor malignancy grade, so that, when preoperative treatment is an option, radiological imaging may add to pathology in providing the clinician with information that helps to estimate the malignancy grade. Pathologic diagnosis relies on morphology and immunohistochemistry. It should be complemented by molecular pathology [fluorescent *in situ* hybridisation (FISH), reverse transcription–polymerase chain reaction (RT–PCR)], to be performed in a laboratory enrolled in an external quality assurance program, in particular when the clinical pathologic presentation is unusual or the histologic diagnosis is doubtful. The tumor sample should be fixed in formalin (Bouin fixation should be avoided, since it may impair the feasibility of molecular analysis). Collection of fresh frozen tissue and tumor imprints (touch preps) is encouraged because new molecular pathology assessments may become available at a later date and could be made in the patient's interest. Informed consent for tumor banking should be sought that allows for later analysis and research, as long as this is allowed by local and national guidelines.

Tumor site should be properly recorded. Tumor size and tumor depth (in relation to the muscular fascia) should be recorded, since they entail a prognostic value, along with the tumor malignancy grade.

staging and risk assessment

The pathology report should include an appropriate description of tumor margins (i.e. the status of inked margins and the distance between tumor edge and the closest inked

*Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganella-Lugano, Switzerland;
E-mail: clinicalrecommendations@esmo.org

Approved by the ESMO Guidelines Working Group: August 2003, last update February 2009. This publication supercedes the previously published version—Ann Oncol 2008; 19 (Suppl 2): ii89–ii93.

Conflict of interest: Dr Casali has reported that he received honoraria and travel coverage for medical meetings from PharmaMar. He had a consultancy role with Ariad Merck, Glaxo and Sanofi Aventis. He is currently conducting research sponsored by PharmaMar, Ariad Merck, Johnson & Johnson, Glaxo and Sanofi Aventis. Dr Jost and Dr Sleijfer have reported no conflicts of interest. Dr Verweij has not reported any conflicts of interest. Prof. Blay has reported that he is currently conducting research sponsored by Novartis, Pfizer, GSK, Pharmamar, Roche and that he received honoraria and research grants from these companies. He has also reported that he is a member of the speakers' bureau for Novartis and Pfizer.

margins). This allows the assessment of marginal status (i.e. whether the minimum margin is intralesional, marginal, wide and distances from surrounding tissues). The pathologic assessment of margins should be made in collaboration with the surgeon.

The surgical report should provide details on the surgical conduct with regard to possible contaminations (i.e. it should mention whether the tumor was opened, etc.).

If preoperative treatment was carried out, the pathology report should include a tumor response assessment. In contrast to osteosarcoma and Ewing's family of tumors, however, no validated system is available at present in this regard, and no percentage of residual 'viable cells' is considered to have a specific prognostic significance. This depends on several factors, including the presence of non-treatment-related necrosis and hemorrhage and the heterogeneity of post-treatment changes. A multidisciplinary judgement is recommended, involving the pathologist and the radiologist.

A chest computed tomography (CT) scan is mandatory for staging purposes. Depending on the histological type and other clinical features, further staging assessments may be recommended (e.g. regional lymph node assessment for synovial sarcoma or epithelioid sarcoma, abdominal CT scan for myxoid liposarcoma, etc.). The American Joint Committee on Cancer (AJCC)/International Union against Cancer (UICC) staging classification system stresses the importance of the malignancy grade in sarcoma. However, its use in routine practice is limited. In addition to grading, other prognostic factors are tumor size and tumor depth. Of course, tumor resectability is also important.

treatment

Soft tissue sarcomas are ubiquitous in their site of origin, and are often treated with multimodality treatment.

Multidisciplinary treatment planning is therefore mandatory in all cases (involving pathologists, radiologists, surgeons, radiation therapists, medical oncologists and pediatric oncologists if applicable). This should be carried out in reference centres for sarcomas and/or within reference networks sharing multidisciplinary expertise. These centres are involved in ongoing clinical trials, in which sarcoma patients' enrolment is highly encouraged. This centralized referral should be pursued as from the time of the clinical diagnosis of a suspect sarcoma. In practice, referral of all patients with a lesion likely to be a sarcoma would be recommended. Practically, this would mean referring all patients with a deep mass of soft tissues, or with a superficial lesion of soft tissues having a diameter of >5 cm.

limited disease

Surgery is the standard treatment for all patients with adult-type, localized soft tissue sarcomas. It should be performed by a surgeon specifically trained in the treatment of this disease. The standard surgical procedure is a wide excision, complemented by radiation therapy as standard treatment of intermediate-high grade, deep tumors with a diameter of >5 cm [II, A]. This implies removing the tumor with a rim of normal

tissue around. One centimeter has been selected as a cut-off in some studies, but it is important to realize that the margin can be minimal in the case of resistant anatomic barriers, such as muscular fasciae, periostium and perineurium. A marginal excision may be acceptable as an individualized option in highly selected cases, in particular for extracompartmental atypical lipomatous tumors.

While radiation therapy as an adjuvant to surgery is a standard for intermediate-high grade, deep tumors with a diameter of >5 cm, it is an option in selected cases of deep lesions ≤5 cm or low-grade tumors. Compartmental resection of an intracompartmental tumor, if performed, does not require adjuvant radiation therapy. Radiation therapy should be administered postoperatively, with the best technique available, at a dose of 50–60 Gy, with fractions of 1.8–2 Gy, possibly with boosts up to 66 Gy, depending on presentation and quality of surgery. Alternatively, radiotherapy may be carried out preoperatively, normally using a dose of 50 Gy. Intraoperative radiation therapy (IORT) and brachytherapy are options in selected cases.

Data have been provided that adjuvant chemotherapy might improve, or at least delay, distant and local recurrence in high-risk patients. A recent meta-analysis found a statistically significant, limited benefit in terms of both survival and relapse-free survival. However, studies are conflicting, and a final demonstration of efficacy is lacking. It is also unknown whether it may be especially beneficial in specific subgroups. Therefore, adjuvant chemotherapy is not standard treatment in adult-type soft tissue sarcomas, and can be proposed as an option to the high-risk individual patient (having a G2–3, deep, >5 cm tumor) for shared decision-making in conditions of uncertainty [II, C]. The histological type may be considered in the decision-making, since some types are felt to be more chemosensitive, whereas others are less so. If the decision is made to use chemotherapy as upfront treatment, it may well be used preoperatively, at least in part. A local benefit may be gained, facilitating surgery. In one large randomized phase III study (in patients with G2–3, deep, >5 cm soft tissue sarcomas), regional hyperthermia in addition to systemic chemotherapy was associated with a local and disease-free survival advantage.

Re-operation should be considered in case of R1 resections, if adequate margins can be achieved without major morbidity, taking into account tumor extent and tumor biology (e.g. it may be spared in extracompartmental atypical lipomatous tumors, etc.). In the case of R2 surgery, re-operation is mandatory, possibly with preoperative treatments if adequate margins cannot be achieved or surgery is mutilating. In the latter case, the use of multimodal therapy with less radical surgery requires a shared decision-making with the patient under conditions of uncertainty. Plastic repairs and vascular grafting should be used as needed, and the patient should be properly referred if necessary. Radiation therapy will obviously follow marginal or R1–R2 excisions, if these cannot be rescued through re-excision, even outside the usual indications. In non-resectable tumors, or those amenable only to mutilating surgery (in this case, on an individualized basis after sharing the decision with the patient in conditions of uncertainty), chemotherapy and/or radiotherapy, or isolated hyperthermic

limb perfusion with tumor necrosis factor- α (TNF α) + melphalan, if the tumor is confined to an extremity, or regional hyperthermia combined with chemotherapy are options.

Regional lymph node metastases should be distinguished from soft tissue metastases involving lymph nodes. They are rare, and constitute an adverse prognostic factor in adult-type soft tissue sarcomas. More aggressive treatment planning is therefore felt to be appropriate for these patients, although there is a lack of formal evidence to indicate that this improves clinical results. Surgery through wide excision (mutilating surgery is exceptionally done given the prognosis of these patients) may be coupled with adjuvant radiation therapy and adjuvant chemotherapy for sensitive histological types, as standard treatment for these presentations. Chemotherapy may be administered as preoperative treatment, at least in part. These treatment modalities adding to surgery should not be viewed as truly 'adjuvant', the context being in fact that of a likely systemic disease. In one large randomized phase III study (in patients with G2–3, deep, >5 cm soft tissue sarcomas), regional hyperthermia in addition to systemic chemotherapy was associated with a local and disease-free survival advantage. Isolated limb perfusion may be an option in this patient population, along with chemotherapy and radiation therapy.

The standard approach to local relapse parallels the approach to primary local disease, except for a wider resort to preoperative or postoperative radiation therapy, if not previously performed.

extensive disease

In the case of synchronous lung metastases without extrapulmonary disease, standard treatment is chemotherapy [IV, B]. Especially when a tumor response is achieved, surgery of completely resectable lung metastases may be offered as an option. Metachronous resectable, and reasonably limited, lung metastases without extrapulmonary disease are managed with complete excision of all visible lesions as standard treatment [IV, B]. Chemotherapy may be added as an option, taking into account the prognostic factors (a short previous free interval and a high number of lesions are adverse factors, encouraging the addition of chemotherapy), although there is a lack of formal evidence that this improves results. Chemotherapy is preferably given before surgery, in order to assess tumor response and thus modulate the length of treatment.

Extrapulmonary disease is treated with chemotherapy as standard treatment [I, A]. In highly selected cases surgery of responding metastases, whether pulmonary or possibly extrapulmonary, may be offered as an option following a multidisciplinary evaluation, taking into consideration their site and the natural history of the disease in the individual patient. Best supportive care may be another option in selected cases.

Standard chemotherapy is based on anthracyclines as first line treatment [I, A]. There is no formal demonstration that multiagent chemotherapy is superior to single-agent chemotherapy with doxorubicin alone. However, a higher response rate may be expected, in particular in a number of

sensitive histological types, according to several, although not all, randomized clinical trials.

Therefore, multiagent chemotherapy with doxorubicin plus ifosfamide may be the treatment of choice, especially when a tumor response is felt to be able to give an advantage and the performance status is good. Dacarbazine may be added to the regimen. In angiosarcoma, taxanes are an alternative option, given their high antitumor activity in this specific histological type [IV, B]. Taxanes are obviously an option also for second-line chemotherapy in this subtype. Imatinib is standard medical therapy for those rare patients with dermatofibrosarcoma protuberans who are not amenable to surgery or with metastases deserving medical therapy [IV, B].

Patients who have already received chemotherapy may be treated with ifosfamide, if they did not receive it previously. High-dose ifosfamide may be an option also for patients who have already received standard-dose ifosfamide [IV, C]. Trabectedin is a second-line option [II, B]. It has proved effective in leiomyosarcoma and liposarcoma. In myxoid liposarcoma a peculiar pattern of tumor response has been reported, with an early phase of tissue changes preceding tumor shrinkage. Responses have been obtained in other histological types, including synovial sarcoma. Randomized evidence was provided that gemcitabine + docetaxel is more effective than gemcitabine alone as second-line chemotherapy [II, D]. Gemcitabine was shown to have antitumor activity in leiomyosarcoma also as a single agent. Dacarbazine has some activity as second-line therapy (possibly mostly in leiomyosarcoma). Best supportive care is an option for pretreated patients with advanced soft tissue sarcoma, all the more if further-line therapies have already been used in the patient.

follow-up

There are no published data supporting specific policies for follow-up of surgically treated patients with localized disease. Relapses most often occur to the lungs. The malignancy grade likely affects the speed at which relapses may take place. The risk assessment based on tumor grade, tumor size and tumor site may help in choosing the routine follow-up policy. High-risk patients generally relapse within 2–3 years, while low-risk patients may relapse later, although it is less likely. Early detection of local or metastatic recurrence to the lungs may have prognostic implications, and lung metastases are asymptomatic at a stage in which they are suitable for surgery. Therefore, routine follow-up may focus on these sites. The best method of follow-up has not been established. Although the use of MRI to detect local relapse and CT to scan for lung metastases is likely to pick up recurrence earlier, it is yet to be demonstrated that this is beneficial or cost effective compared with clinical assessment of the primary site and regular chest X-rays.

The surgically treated intermediate/high grade patient may be followed every 3–4 months in the first 2–3 years, then twice a year up to the fifth year and once a year thereafter. Low-grade sarcoma patients may be followed for local relapse every 4–6 months, with chest X-rays or CT scan at more relaxed intervals in the first 3–5 years, then yearly.

special presentations and entities

retroperitoneal sarcomas

Core needle biopsies are the standard procedure for diagnosis in retroperitoneal sarcomas. An open biopsy may be an option in selected cases. In both cases, the pathway of the biopsy should be carefully planned to avoid contamination and complications. However, radiological imaging may be sufficient for the diagnosis of lipomatous tumors, if no preoperative treatment is planned. Standard treatment for localized lesions is surgery, which is best performed through a retroperitoneal compartmental resection (i.e. complete excision of the tumor, along with en-bloc visceral resections) [IV, D]. Preoperative treatment may be an option, including radiation therapy, chemotherapy, chemoradiation therapy, regional hyperthermia in addition to chemotherapy. Adjuvant chemotherapy is an option as for high-risk localized soft tissue sarcoma of limbs and superficial trunk.

uterine sarcomas

This group includes leiomyosarcomas, endometrial stromal sarcomas, undifferentiated endometrial sarcomas and pure heterologous sarcomas. Carcinosarcomas (malignant Mullerian mixed tumors) are mixed epithelial and mesenchymal neoplasms, whose treatment may well follow their mainly epithelial nature.

Standard treatment for all these tumors, when localized, is total abdominal hysterectomy, although for endometrial stromal sarcomas bilateral salpingo-oophorectomy is generally performed, due to the hormonal sensitivity of these tumors, and lymphadenectomy may be an option, given the possible higher incidence of nodal involvement [IV, D]. As far as leiomyosarcomas and high-grade undifferentiated sarcomas are concerned, bilateral salpingo-oophorectomy, particularly in premenopausal women, as well as lymphadenectomy, is not demonstrated to be useful in the lack of macroscopic involvement. Radiation therapy has not improved survival and relapse-free survival in a randomized setting, although retrospective studies suggested a possible decrease in local relapses. Therefore, its use as an adjuvant to surgery may only be an option in selected cases, after shared decision-making with the patient [III, C]. The systemic treatment of metastatic endometrial stromal sarcomas exploits their sensitivity to hormonal therapies [V, D]. Therefore, progestins are generally used, along with Gn-RH analogues and aromatase inhibitors. Tamoxifen is contraindicated, as well as hormonal replacement therapy containing estrogens. Surgery of lung metastases is an option, given the natural history of the disease. The systemic treatment of leiomyosarcomas, undifferentiated endometrial sarcomas and pure heterologous sarcomas parallels that for adult-type soft tissue sarcomas.

desmoid-type aggressive fibromatosis

Standard treatment for primary disease, if amenable to surgery without significant functional losses, is wide excision [IV, B]. In those cases in which only marginal excision can be performed, postoperative radiation therapy is an option, after sharing the decision with the patient in conditions of uncertainty,

considering the possible occurrence of radiation-related high grade sarcomas in a non-metastasizing disease. Observation is another option in selected cases, after shared decision-making with the patient, taking into account the indolent natural history of some clinical presentations. For primary disease only amenable to surgery with significant functional losses, wide excision is an option, along with radiation therapy, observation, isolated limb perfusion (if the lesion is confined to an extremity) or systemic therapy (see below) [V, D]. The same applies to recurrent disease. For the inoperable disease, radiation therapy, ILP (if the lesion is confined to an extremity), and systemic therapies are options, along with observation [V, D]. Systemic therapies include: hormonal therapies (tamoxifen, toremifene, Gn-RH analogues), non-steroidal anti-inflammatory drugs; low-dose chemotherapy, such as methotrexate + vinblastine or methotrexate + vinorelbine; low-dose interferon; imatinib; full-dose chemotherapy (using regimens active in sarcomas). It is reasonable to employ the less toxic therapies before the more toxic in a stepwise fashion.

notes

Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty.

These Clinical Recommendations update those formulated in 2008 following a consensus process based on a consensus event organized by ESMO in Lugano in October 2007. The consensus update in early 2009 and the previous event involved the same experts from the community of the European sarcoma research groups and from some sarcoma reference centres outside Europe. Their names are indicated hereafter. The text reflects an overall consensus among them, although each of them may not necessarily find it consistent with his/her own views. The EU-funded network of excellence CONTICANET (CONnective TIssue CAncers NETwork) supported the consensus process.

consensus panel

Paolo G. Casali, Milano, Italy (coordinating author); Jean-Yves Blay, Lyon, France (coordinating author).

Massimo Aglietta, Torino, Italy; Thor Alvegard, Lund, Sweden; Larry Baker, Ann Arbor, USA; Robert Benjamin, Houston, USA; Martin Blackstein, Toronto, Canada; Sylvie Bonvalot, Paris, France; Ioannis Boukovinas, Thessaloniki, Greece; Binh Bui, Bordeaux, France; Angela Buonadonna, Aviano, Italy; Paola Collini, Milano, Italy; Alessandro Comandone, Torino, Italy; Enrique de Alava, Salamanca, Spain; Maria Debiec-Rychter, Leuven, Belgium; Angelo Paolo Dei Tos, Treviso, Italy; George D. Demetri, Boston, USA; Palma Dileo, Milano, Italy; Mikael Eriksson, Lund, Sweden; Andrea Ferrari, Milano, Italy; Stefano Ferrari, Bologna, Italy; Sergio Frustaci, Aviano, Italy; Xavier Garcia-Del-Muro, Barcelona, Spain; Robert Grimer, Birmingham, UK; Alessandro Gronchi, Milano, Italy; Federica Grosso, Milano, Italy; Pancras

Hogendoorn, Leiden, the Netherlands; Peter Hohenberger, Mannheim, Germany; Rolf Issels, Munich, Germany; Svetlana Jezdic, Lugano, Switzerland; Heikki Joensuu, Helsinki, Finland; Lorenz Jost, Bruderholz, Switzerland; Ian Judson, London, UK; Michael Leahy, London, UK; Serge Leyvraz, Lausanne, Switzerland; Axel Le Cesne, Paris, France; Robert Maki, New York, USA; Javier Martin, Mallorca, Spain; Joan Maurel, Barcelona, Spain; Pierre Meeus, Lyon, France; Michael Montemurro, Lausanne, Switzerland; Patrizia Olmi, Milano, Italy; Shreyas Patel, Houston, USA; Piero Picci, Bologna, Italy; Andres Poveda, Valencia, Spain; Peter Reichardt, Berlin, Germany; Martin H. Robinson, Sheffield, UK; Piotr Rutkowski, Warsaw, Poland; Marcus Schlemmer, München, Germany; Patrick Schoffski, Leuven, Belgium; Stefan Sleijfer, Rotterdam, the Netherlands; Kirsten Sundby Hall, Oslo, Norway; Elena Tamborini, Milano, Italy; Jonathan Trent, Houston, USA; Frits Van Coevorden, Amsterdam, the Netherlands; Martine Van Glabbeke, Brussels, Belgium; Allan Van Oosterom, Leuven, Belgium; Jaap Verweij, Rotterdam, the Netherlands; Eva Wardelmann, Bonn, Germany; John Zalberg, Melbourne, Australia.

literature

1. Antman K, Crowley J, Balcerzak SP et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. *J Clin Oncol* 1993; 11: 1276–1285.
2. Bonvalot S, Rivoire M, Castaing M et al. Primary retroperitoneal sarcomas: a multivariate analysis of surgical factors associated with local control. *J Clin Oncol* 2009; 27: 31–37.
3. Eggermont AMM. Isolated limb perfusion in the management of locally advanced extremity soft tissue sarcoma. *Surg Oncol Clin N Am* 2003; 12: 469–483.
4. Fata F, O'Reilly E, Ilson D et al. Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. *Cancer* 1999; 86: 2034–2037.
5. Garcia-Carbonero R, Supko JG, Manola J et al. Phase II and pharmacokinetic study of ecteinascidin 743 in patients with progressive sarcomas of soft tissues refractory to chemotherapy. *J Clin Oncol* 2004; 22: 1480–1490.
6. Gronchi A, Lo Vullo S, Fiore M et al. Aggressive surgical policies in a retrospectively reviewed single-institution case series of retroperitoneal soft tissue sarcoma patients. *J Clin Oncol* 2009; 27: 24–30.
7. Grosso F, Jones RL, Demetri GD et al. Efficacy of trabectedin (ecteinascidin-743) in advanced pretreated myxoid liposarcomas: a retrospective study. *Lancet Oncol* 2007; 8: 595–602.
8. Hensley ML, Maki R, Venkatraman E et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. *J Clin Oncol* 2002; 20: 2824–2831.
9. Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. *Gynecol Oncol* 2008; 109: 329–334.
10. Issels RD, Lindner LH, Wust P et al. Regional hyperthermia (RHT) improves response and survival when combined with systemic chemotherapy in the management of locally advanced, high grade soft tissue sarcomas (STS) of the extremities, the body wall and the abdomen: A phase III randomised prospective trial (EORTC-ESHO Intergroup trial) ASCO Ann Meet Proc Part I. *J Clin Oncol* 2007; 25 (Suppl 18): 10009.
11. Janinis J, Patriki M, Vini L et al. The pharmacological treatment of aggressive fibromatosis: a systematic review. *Ann Oncol* 2003; 14: 181–190.
12. Kanjeekal S, Chambers A, Fung MF, Verma S. Systemic therapy for advanced uterine sarcoma: a systematic review of the literature. *Gynecol Oncol* 2005; 97: 624–637.
13. Le Cesne A, Antoine E, Spielmann M et al. High-dose ifosfamide: circumvention of resistance to standard-dose ifosfamide in advanced soft tissue sarcomas. *J Clin Oncol* 1995; 13: 1600–1608.
14. Maki RG, Wathen JK, Patel SR et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002. *J Clin Oncol* 2007; 25: 2755–2763.
15. Pastorino U, McCormack PM, Ginsberg RJ. A new staging proposal for pulmonary metastases. The results of analysis of 5206 cases of resected pulmonary metastases. *Chest Surg Clin N Am* 1998; 8: 197–202.
16. Penel N, Bui BN, Bay JO et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. *J Clin Oncol* 2008; 26: 5269–5274.
17. Pervaiz N, Colterjohn N, Farrokhyar F et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. *Cancer* 2008; 113: 573–581.
18. Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. *Lancet* 1997; 350: 1647–1654.